Case No. 0550-0059.30/4291

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Woudenberg et al.

Serial No.: 08/831,983

Filed: April 2, 1997

For: **DEVICE FOR MULTIPLE ANALYTE DETECTION [AS AMENDED 3/20/98]**

Group Art Unit: 1641

Examiner: Devi, S.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being facsimile transmitted to the Examiner S. Devi in Art Unit 1641 at the U.S. Patent and Trademark Office, fax number 703-308-4242 on

March 8 2004
(Date of Deposit)

Vincent M Powers
Name of Depositing Party

Vincent M Powers
Signature of Depositing Party

Declaration of Kenneth J. Livak Under 37 CFR 1.132

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

I, Kenneth J. Livak, declare and affirm as follows:

1. I am a Principal Scientist at PE Biosystems in Foster City, California.

2. I received a Bachelor of Science Degree in Chemistry from Harvey Mudd College in Claremont, California in 1974 and a Ph.D. Degree in Biochemistry from Harvard University in 1979. I was a postdoctoral fellow at the University of California at San Diego from 1979 to 1982. From 1982 to 1991 I was a Staff Scientist at E.I. du Pont de Nemours and Co. in Wilmington, Delaware. From 1991 to 1994 I was Senior Research Scientist and then Principal Research Scientist (from 1993) at Du Pont Merck Pharmaceutical Co. I have been with PE Biosystems since 1994.

3. I consider my field of specialization to be nucleic acid detection and analysis. I have authored or co-authored numerous scientific journal articles relating to nucleic acids. I am an

inventor in about ten United States patents as well as various pending patent applications and foreign counterparts.

4. In my career, my duties have included extensive experimental work in the areas of DNA sequencing, gene expression, chromosome analysis, mutation detection, characterization of allelic variants, and detection of target nucleic acid sequences. I have personally practiced numerous analytical techniques for characterizing nucleic acids, including hybridization, PCR, and others, using a variety of different experimental formats. I am familiar with the mainstream techniques that have been developed to date for nucleic acid detection or quantitation from my experimental work and from familiarity with the relevant scientific literature.

5. I have reviewed the above-identified patent application, the pending claims, the final Office action dated October 5, 1999, and the references cited therein. From reading the Office action, I understand that the claims were rejected by the Examiner for allegedly being obvious over Fadler et al. (US Patent No. 4,038,151), Wu et al. (US Patent No. 5,612,473), Mitsuhashi et al. (US 5,639,612) and Bouma et al. (US Patent No. 5,585,242). For the following reasons, I disagree with the rejection.

6. Prior to the present invention, many techniques had been proposed for detecting nucleic acids. Generally, solution-phase assays involved performing hybridization or amplification reactions in separate reaction vessels, usually followed by removal of an aliquot of the reaction mixture for analysis by electrophoresis, high-performance liquid chromatography, membrane blotting, etc. In some cases, such as for detection by PCR, multiple target sequences have been amplified within the same reaction mixture, but subject to an increased chance of spurious results.

7. However, for analyzing large numbers of different potential targets in a sample, the tendency has been to use multi-well plates that require individual deposition of sample into each well. Although this has been conducive to automation, such as adaptation to multi-well plate readers, multi-well plates has been limited because of the need for extensive sample manipulation for delivery of the sample to different wells. Furthermore, the sample loading step has required tedious manual pipetting or costly robotic apparatus and the need for carefully controlled conditions to avoid contamination problems. By prolonging assay time, the need for extensive sample loading has reduced the rate of sample throughput. Overall, the lack of a practicable, economically affordable assay format for rapid, simultaneous determination of multiple target nucleic acid

sequences in a single sample has significantly hindered the development and commercialization of nucleic acid assays in the medical diagnostics field.

8. In my opinion, the presently claimed invention constitutes a significant advance in the area of nucleic acid analysis. The invention uses a sample-distribution network having (i) a sample inlet, (ii) two or more detection chambers, and (iii) channel means providing a dead-end fluid connection between each of the chambers and the inlet, with different, sequence-specific polynucleotide binding polymer placed in different chambers for detecting or quantitating different polynucleotide sequences. Evacuation of the network, followed by application of the sample to the inlet, is effective to draw sample by vacuum into each of the chambers. By loading the wells simultaneously, there is a significant savings in time and manipulation. Moreover, with sequence-specific binding polymers already provided in the wells, greater uniformity is achieved both within a given sample as well as between different samples. It can also be seen from considering the above factors that the chance for user error is significantly reduced.

9. Based on my knowledge of the nucleic acid analysis field, and my reading of the references cited in the last Office action, I do not understand how the claimed invention can be considered to have been obvious. On the contrary, I consider the invention to have been anything but obvious given the approaches that existed in the field of nucleic acid analysis as of the first filing date of the invention (April, 1996).

10. The Fadler patent (US 4,038,151) discloses an assay for detecting living microorganisms in a sample. According to Fadler, such microorganisms are detected if they are able to grow in one or more of the various media provided in the various wells.

11. In characterizing Fadler et al., the Examiner suggested that "There is no reason why one skilled in the art would not look to Fadler's disclosure while designing a device for detection of one or more analytes such as polynucleotide sequences which form a part of, or which are contained within the microbes" (final Office action, bottom of page 4). I respectfully disagree. It is one thing to try to detect living cells. It is another to detect or quantify specific polynucleotide sequences. These different objectives are worlds apart.

12. The field of Fadler et al. is microbiology. The problem addressed by Fadler was the identification and quantitation of microorganisms and their susceptibility to antibiotics (column 1, lines 24-29, and Background section overall). The solution offered by Fadler, for microbe

detection, was to provide different dried media that would allow growth of potential contaminating organisms via cell culture using a device having long passageways with discontinuities (column 2 lines 13-18). Fadler et al. does not provide different, sequence-specific polynucleotide binding polymers for detecting or quantitating different polynucleotide sequences in the sample.

13. I can see no suggestion in Fadler of forming a device for specific nucleic acid detecting in accordance with the present invention. Moreover, I do not believe that one of ordinary skill in the nucleic acid analysis would have looked to the field of Fadler et al. to arrive at a solution for specific nucleic acid detection. The Fadler reference is quite old (issued in 1977), yet I was unaware of it until it was brought to my attention in the course of preparing a response to the present Office action.

14. That the invention was not obvious is further shown from consideration of the other references cited in support of the rejection.

15. Wu et al. (US 5,612,473) focuses on a special extraction buffer that is supposed to improve the yield of DNA extracted from cells, for analysis by PCR or other technique. The only devices mentioned, either for nucleic acid hybridization or PCR amplification, are microtiter plates (column 24, lines 4-7) and microfuge tubes of the type used in a Perkin Elmer 9600 thermocycler (e.g., column 24, lines 32-34). There is no disclosure of using a multi-chamber device having the attributes of the present invention.

16. Mitsuhashi et al. (US 5,639,612) discloses a sandwich hybridization assay using probes having melting temperatures within a specific range. The only devices mentioned for running the assay appear to be standard microtiter plates (column 18 lines 30-35). The authors provide no guidance or motivation for modifying such standard apparatus to arrive at a device in accordance with the present invention.

17. Bouma et al. (US 5,585,242) discloses a particular detection technique relating to total internal reflection, for use with a single reaction vessel, as is clear from the figures (e.g., Figs. 1-2).

18. I understand that the other references mentioned in section (8) of the Office action were cited as reflecting the state of the art. Those references teach various devices that are clearly different from the device of the present invention and, if anything, highlight the fact that the present invention would not have been obvious.

19. In summary, I believe that the present invention constitutes a true innovation in the field of nucleic acid analysis that warrants grant of a patent. Prior to the disclosure by the inventors, this device was not known in the field of nucleic acid analysis nor would it have been within ordinary design choice.

20. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

3/2/00
Date

Kenneth J. Livak